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Cryosurgical Ablation of Unresectable Hepatic Metastases

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Background and Objectives: Recent advancements in the technology of cryosurgery along with the development and refinement of intraoperative ultrasound have led to a feasible alternative for some patients with unresectable hepatic malignancy. This paper reports our first year's experience with cryosurgical ablation of unresectable hepatic malignancies.
Methods: From May 1996 to July 1997, 12 patients with colorectal hepatic metastases underwent exploration for possible resection and/or cryosurgery. At surgery, three patients had extensive disease and were not candidates for any surgical treatment, three underwent formal right hepatic lobectomy, five underwent a combination of resection and cryoablation, while one underwent cryoablation alone.
Results: In the six patients who received cryosurgery, the mean number of metastatic lesions was four (range 1–6). The mean number of lesions frozen was two (range 1–4) with a mean size of 2.5 cm. (range 1–5 cm). There were no intraoperative deaths and no major postoperative complications. All patients were discharged home in stable condition with a mean hospital stay of eight days (range 5–14 days). At a mean follow-up of 17.3 months (range 10–22) three patients were alive with disease and three were disease free.
Conclusions: Cryosurgical ablation is a safe method of treating unresectable hepatic malignancies and it may extend survival in carefully selected patients. *J. Surg. Oncol. 1998;68:242–245.*

KEY WORDS: cyrosurgery; hepatic metastases; unresectable

INTRODUCTION

Colorectal cancer accounts for 135,000 new cases and 60,000 deaths annually in the United States [1]. Approximately 50% have metastatic disease at the time of diagnosis or develop recurrence following surgery, of which 50–75% have metastases in the liver, and 20% will have metastases confined to the liver [2]. An estimated 5–10% of all patients with colon cancer will develop liver metastases that may be amenable to resection [3]. Surgical resection is potentially curative, however, anatomic considerations or the general medical condition often preclude this approach. Cryosurgical ablation of hepatic metastases from colorectal adenocarcinoma is a well-described technique, particularly in those patients whose tumors are not amenable to resection [4]. While the effect of cryosurgery on long-term survival is yet to be established because of short follow-up intervals, the relative safety of this procedure is well documented. In this report, we review our first year's experience with cryosurgical ablation of unresectable hepatic metastases.

MATERIALS AND METHODS

All patients evaluated for hepatic malignancies from May 1, 1996, through July 31, 1997, were retrospectively reviewed. All patients underwent a complete preoperative evaluation to include physical examination, colonic evaluation with barium enema or colonoscopy, chest radiography or computed tomography (CT), and abdominal CT. Those patients without evidence of extrahepatic

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metastatic disease were considered for resection and/or cryosurgical ablation of the hepatic malignancy. Exploratory laparotomy was performed through a small right subcostal incision. A thorough evaluation of the abdomen, including biopsy with frozen section of any suspicious extrahepatic lesions, was performed. If there was no evidence of extrahepatic disease, the incision was extended to a bilateral subcostal or ''chevron'' incision. Upward extension in the midline was performed when necessary. After complete mobilization of all hepatic attachments, intraoperative ultrasound (HDI 3000, ATL Corp., Los Angeles, CA) was performed by the principal investigator (PSD). Unconfirmed metastases were biopsied with a Tru-Cut needle and a frozen section diagnosis was made. After the extent of disease was established, these patients either underwent resection, cryosurgical ablation, a combination of both or no intervention at all. Resectability was determined by location, confinement to one lobe and not in contact with major vessels or ducts, number of lesions, and comorbid factors prohibiting formal lobectomy. Those lesions that were resectable were resected in standard fashion with either wedge resection with a 1-cm margin, formal segmental resection, or formal hepatic lobectomy. Cryosurgery was performed with the LCS 3000 (Candella Inc., Wayland, MA) cryosurgical unit. Probes were inserted under direct ultrasound guidance with the tip placed centrally in the lesion. Depending on tumor size, 10-, 5-, or 3-mm probes were used. For larger or irregular-shaped tumors, multiple simultaneous probes were used. Cryosurgery proceeded with ice ball growth monitored by ultrasound. All freezes were done at probe tip temperatures from −150 to −170°C. Once the tumor and a surrounding 1-cm rim of normal hepatic parenchyma were encompassed in the ice ball the freeze process was maintained for an additional 15–20 min. The ice ball was then thawed until the probes became free and a second freeze was then performed for 5–10 min. The ice ball was then thawed and, once the probes were free, they were quickly removed and the cryohole was filled with Gelfoam hemostatic agent or platelet gel. Simultaneous freezes on the same or different tumors were performed using the five-port system of the cryosurgery unit. Patients went to the ICU or surgical ward postoperatively depending on their condition. All patients were discharged when tolerating a regular diet and had adequate pain control. Routine postoperative laboratory tests were performed daily for 3 days, including complete blood counts (CBC) and chemistry profiles. A chest radiograph was performed postoperatively in the recovery room and then as clinically indicated. All patients received perioperative antibiotic therapy. Intraoperative blood loss and fluid replacement were recorded.

RESULTS

Twelve patients with hepatic metastases were evaluated for surgical resection and/or hepatic cryosurgical ablation. The mean age was 55.5 years (range 45–66 years). All patients had known colorectal malignancies, eleven adenocarcinomas and one carcinoid tumor. The mean time from resection of the primary colorectal carcinoma to diagnosis of hepatic metastasis was 16 months (range 0–48 months). Metastatic disease was detected by rising carcinoembryonic antigen (CEA) and subsequent CT scan of the abdomen. Chest radiography or CT scan was negative for a pulmonary metastasis, and abdominal CT scans showed disease confined to the liver in all patients. At exploration, extrahepatic metastatic disease was identified in two patients. One patient had extensive hepatic disease (>8 lesions) demonstrated with intraoperative ultrasound that was not identified on a preoperative abdominal CT scan. The remaining nine patients were considered suitable for hepatic resection or cryosurgical ablation according to the previously mentioned criteria. Eight patients had metastatic adenocarcinoma, and one patient had a metastatic carcinoid tumor. Three patients underwent successful right hepatic lobectomy. Six patients underwent cryosurgical ablation, five accompanied by some type of resection. For those undergoing cryosurgery, the mean number of metastatic lesions was four (range 1–6), with a mean size of 2.5 cm (range 1–5 cm). The mean number of lesions frozen was two (range 1–4). There were no intraoperative deaths or major complications. Operative time ranged from 3 to 6 h, depending on the number of lesions treated. Mean blood loss was 617 ml (range 200–1,300 ml). Two patients who received combined resection and cryoablation required 2 units of packed red blood cells. Two units of fresh frozen plasma were given to four patients. Five patients were observed in the surgical intensive care unit for 24 h, and one was admitted to the general surgical ward without a stay in the intensive care unit (ICU). All cryosurgery patients had transient thrombocytopenia (platelet counts of <100,000), all of which were self-limiting and none required platelet transfusion. Postoperatively, a right pleural effusion was documented in two patients. One of these became symptomatic and required thoracentesis. The mean length of hospital stay was 8 days (range 5–14 days). All patients were followed by the principal investigator (P.S.D.), with a mean follow-up of 17 months (range 10–22 months). At last follow-up all six patients were alive. Three were alive with disease and three remained disease free. The data for each patient are presented in Table I. All had a good performance status.

DISCUSSION

The natural history of patients with hepatic metastases from colorectal cancer is dependent on the extent of liver metastases and extrahepatic disease. Hughes et al. [5] in a collective review of 673 patients with untreated hepatic metastases reported a mean survival of 6–13 months. Considering only untreated patients with isolated hepatic

TABLE I. Cryosurgical Ablation of Unresectable Hepatic Metastases: Patient Characteristics

Patients	1	2	3	4	5	6	Mean
Age	45	54	64	56	66	48	55.5
Total lesions	4	1	4	4	6	5	4
Frozen lesions	1	1	1	2	3	4	2
Resection	Yes	No	Yes	Yes	Yes	Yes	—
Blood loss (ml)	500	400	200	300	1,000	1,300	617
Complications	0	PE[a]	0	0	0	PE	—
Disease-free survival (mo)	19	17	16	6	6	0	12.8
Overall survival (mo)	19	17	16	22	20	10	17.3

[a]PE, pleural effusion.

metastases, the mean survival was 18 months and the 5-year survival was 1%. Systemic chemotherapy generally achieves a response rate of 20% in those with hepatic metastases, but no significant survival advantage is observed as compared with those who receive no treatment at all [6]. Regional chemotherapy infused directly into the hepatic artery produces response rates of 40–80%. However, several prospective randomized trials have not demonstrated a significant survival advantage when compared to systemic chemotherapy [7–9]. Surgical resection has the potential for cure and those who are cleared of all hepatic disease have a 5-year survival of 25–35% [2,5]. In a recent review of 123 patients who underwent a hepatic resection for metastatic colorectal cancer by Taylor et al. [10], a 5-year survival of 47% was reported for individuals with a solitary metastatic lesion, while those with multiple lesions, but less than patients had a 5-year survival of 17%. Unfortunately, the value of surgical resection is limited to the minority of individuals with disease confined to the liver and further diminished by the finding at exploration of extrahepatic spread or diffuse hepatic involvement. In reality, only 5–10% of those with colorectal cancer develop hepatic metastases that are amenable to surgical resection.

Cryosurgery offers an alternative approach for some patients who have metastatic disease confined to the liver but are unable to undergo a resection because of anatomic considerations or prohibitive comorbid factors. Additionally, cryosurgery can be used in conjunction with surgical resection in instances in which complete resection is not feasible. In our series, 12 patients underwent metastatic workup and appeared to have disease confined to the liver; however, at exploration, only three were amenable to resection for clearance of all hepatic disease. Two-thirds (six of nine) of those deemed unresectable were amenable to cryoablation alone or a combination of resection and cryoablation.

The first attempt to destroy malignant tumors with a freezing technique occurred in 1845, when James Arnott, a English physician used iced saline to reduce the size of breast and neck tumors [11]. By the turn of the century, cryosurgical techniques were developed and successfully applied in the field of dermatology. The first closed liquid nitrogen cryosurgery system was developed in 1963, by Cooper [12] and was successfully used to treat Parkinson's disease. Cooper also speculated that cryosurgery might be used in the future to treat primary and metastatic liver tumors. The technical feasibility of hepatic cryosurgery was demonstrated by Gage and Dutta [13] in 1979. Their work in canine models demonstrated that large volumes of hepatic tissue could be frozen and left in situ with no detrimental sequelae. Reports of human trials also appeared in the literature around this time; notably Zhou et al. [14] reported 35 patients with unresectable hepatocellular carcinomas who underwent cryosurgery. A 2-year survival of 24.3% was observed, while there were no operative deaths or major complications such as bleeding, bile leakage, tumor rupture, or infection.

During the early experience with hepatic cryosurgery, surgeons relied on palpation and visualization to identify and treat tumors often leaving lesions deep in the parenchyma unrecognized and therefore untreated. Intraoperative ultrasound, although described in 1963, by Knight and Newell [15] failed to gain wide acceptance until the technique was reintroduced in 1981, by Makuuchi et al. [16]. Modern intraoperative ultrasound technology has revolutionized hepatic cryosurgery. Surgeons are now able to image deep into the liver parenchyma to determine accurately the extent of hepatic disease and the relationship of a particular lesion to a major vascular structure or major bile duct. Additionally, lesions can be monitored during the freeze process to ensure an adequate margin [17]. The value of intraoperative ultrasound in the surgical treatment of hepatic malignancy is well demonstrated in a report by Staren et al. [18]. In their review of 59 patients who underwent exploration with intraoperative ultrasound, 19 patients (32%) were found to have lesions not evident during their preoperative evaluation. If the lesions that were clinically apparent at exploration were excluded, eight patients (14%) had tumors only recognized by intraoperative ultrasound. In this series, the preoperative plan for surgery was altered in 20 patients (34%).

Currently, cryosurgery is an accepted alternative for those with unresectable hepatic malignancies. The overall safety, including morbidity and operative mortality, is well documented [19,20]. Increased survival has also been reported for cryosurgical treatment of primary and metastatic tumors. Zhou et al. [21] reported a series of 60 patients in 1989, who underwent cryosurgical treatment of hepatocellular carcinomas and noted a 5-year survival of 37.5%, while Kuramoto [22] during the same year reported a 5-year survival of 25% in 29 patients. Ravikumar et al. [4] reported a series in 1991, with 32 patients predominately with unresectable colorectal metastases and noted at a median follow-up of 24 months, 62% were

alive, and 28% were disease free. Six patients in the study had known residual disease at the time of surgery and if excluded, result in a 78% survival, with 39% remaining disease free.

Our study documents results similar to those reported in other studies. With a mean follow-up of 17 months, three of five patients who were treated cryosurgically remain disease free. (Not including one patient with carcinoid tumors that was treated as a palliative measure and was left with residual disease.) Postoperatively, extrahepatic metastasis occurred in one of our patients and recurrence at the site of cryoablation in another. This has been reported in other studies of both resection and cryosurgical ablation and is often the cause of death in these patients [10,23]. Both patients are being treated with systemic chemotherapy and remain alive with disease. The addition of regional chemotherapy postoperatively may reduce the occurrence of hepatic relapse in those who undergo cryosurgery; this approach is currently being investigated.

Cryosurgery was well tolerated by all our patients. There were no intraoperative deaths or major complications. Blood loss and transfusion requirements were less than that reported for resection of metastases. Intraoperative hepatic ''cracking'' was not seen in our series, although this serious complication is well reported and is associated with ablation of large lesions. Postoperative thrombocytopenia and coagulopathy were seen in all patients and was self-limiting and did not requiring therapeutic intervention. This phenomenon is seen often with cryosurgery and most likely is related to a consumptive coagulopathic process arising from the rapid release of tumor cytokines. Two patients developed pleural effusions and one required thoracentesis. The rapid reduction of tumor markers in noncolorectal metastasis after cryoablation has recently been reported by Bilchik and colleagues [24]. This was evident in our patient with a carcinoid tumor who had a rapid reduction postoperatively in frequency of diarrhea and flushing without somatostatin therapy.

The application of cryosurgery to assist with a hepatic resection has also been reported. The technique of freezing the metastasis with subsequent segmental resection while the tissue is frozen may aid with attaining good surgical margins as reported by Polk et al. [25]. The use of a flat probe to increase surgical margins in areas of grossly close or microscopically positive margins has also been reported [23]. This technique can add an additional centimeter to the resection margin in cases where further resection may be anatomically difficult. While cryosurgery should not replace hepatic resection, it can be used alone or in combination with surgery to offer improved survival with acceptable morbidity in patients with unresectable hepatic malignancies. Our study supports the growing literature regarding safety and efficacy of cryosurgery in the management of unresectable hepatic tumors.

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